201-14550

June 17, 2003

Ms. Christine Todd Whitman, Administrator
US EPA
PO Box 1473
Merrifield, VA 22116

Attn: Chemical Right-to-Know Program

RE: HPV Chemical Challenge Program, AR-201

Dear Ms Whitman:

On behalf of Eastman Chemical Company, I am pleased to submit the test plan and robust summaries for Dimethyl-1,4-cyclohexanedicarboxylate (DMCD; CAS No.: 94-60-0). My company had agreed to sponsor this chemical and provide the Agency with the enclosed information in the year 2003.

Enclosed with this letter is a computer diskette containing the test plan and robust summaries in Adobe Acrobat (.pdf) format. The HPV registration number for Eastman Chemical is *

We understand this information will be posted on the internet for comments for a period of 120 days. Please forward comments to me at the above address.

Sincerely,

James A. Deyo D.V.M., Ph.D., D.A.B.T.
Senior Associate

HIGH PRODUCTION VOLUME (HPV) CHALLENGE PROGRAM

TEST PLAN
FOR
DIMETHYL 1,4-CYCLOHEXANEDICARBOXYLATE
(CAS NO.: 94-60-0)

PREPARED BY:

EASTMAN CHEMICAL COMPANY

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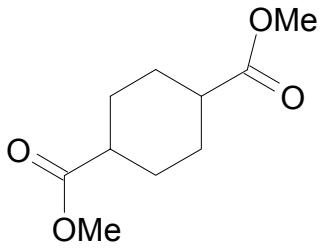
OVERVIEW

The Eastman Chemical Company hereby submit for review and public comment the test plan for dimethyl-1,4-cyclohexanedicarboxylate (DMCD; CAS No.: 94-60-0) under the Environmental Protection Agency's (EPA) High Production Volume (HPV) Chemical Challenge Program. The chemical represented by this CAS number consist of a mixture of both *cis*- and *trans*- isomers. In preparing this test plan, Eastman has given careful consideration to the principles contained in the letter the EPA sent to all HPV Challenge Program participants on October 14, 1999. As directed by EPA in that letter, we have sought to maximize the use of existing data for scientifically appropriate related chemicals and structure-activity-relationships. Additionally, and also as directed in EPA's letter, in analyzing the adequacy of existing data, the Panel has conducted a thoughtful, qualitative analysis rather than use a rote checklist approach.

It is the intent of our company to adequately fulfill all endpoints in the Screening Information Data Set for the physicochemical, environmental fate, ecotoxicity test, and human health effects endpoints. This will be accomplished using existing data on DMCD (CAS No.: 94-60-0), DMCD as a pure *trans*- isomer (CAS No.: 3399-22-2), or with data on a structural analog, 1,4-Cyclohexanedicarboxylic acid (CAS No.: 1076-97-7). In addition, EPA-acceptable predictive computer models and values from reputable textbooks are used to fulfill various endpoints. We believe that, in total, these data are adequate to fulfill all the requirements of the HPV program without need for the conduct any new or additional tests.

DMCD is a colorless partially crystallized liquid capable of being manufactured to a high degree of purity. The primary use for this compound is as an industrial intermediate in the manufacture of various types of polymers and resins. Accordingly, as an industrial intermediate used in the synthesis of polymers, exposure to the environment and general public is essentially non-existent. DMCD, as supplied by Eastman Chemical Company, is lawful for use as a monomer for polyesters used as a component of food packaging adhesive under the conditions defined in regulations administered by the U. S. Food and Drug Administration at 21 CFR 175.105.

TEST PLAN SUMMARY

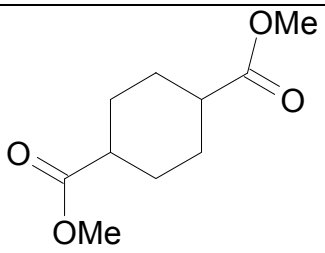
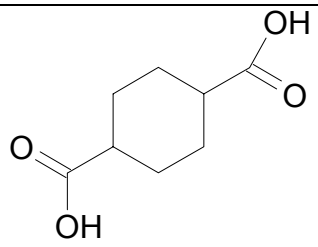
CAS No. 94-60-0 	Information	OECD Study	Other	Estimation	GLP	Acceptable	New Testing Required
STUDY	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N	Y/N
PHYSICAL-CHEMICAL DATA							
Melting Point	Y	-	Y	Y	N	Y	N
Boiling Point	Y	-	Y	-	N	Y	N
Vapor Pressure	Y	-	Y	Y	N	Y	N
Partition Coefficient	Y	-	Y	Y	N	Y	N
Water Solubility	Y	-	Y	Y	N	Y	N
ENVIRONMENTAL FATE ENDPOINTS							
Photodegradation	Y	-	-	Y	N	Y	N
Stability in Water	Y	-	-	Y	N	Y	N
Biodegradation	Y[1]	Y	-	-	Y	Y	N
Transport between Environmental Compartments (Fugacity)	Y	-	-	Y	N	Y	N
ECOTOXICITY							
Acute Toxicity to Fish	Y[1]	-	Y	-	N	Y	N
Acute Toxicity to Aquatic Invertebrates	Y[1]	-	Y	-	N	Y	N
Toxicity to Aquatic Plants	Y	Y	-	-	Y	Y	N
TOXICOLOGICAL DATA							
Acute Toxicity	Y	Y	-	-	Y	Y	N
Repeated Dose Toxicity	Y[2]	Y	-	-	Y	Y	N
Genetic Toxicity – Mutation	Y[2]	-	Y	-	Y	Y	N
Genetic Toxicity – Chromosomal Aberrations	Y[2]	-	Y	-	Y	Y	N
Developmental Toxicity	Y	Y	-	-	Y	Y	N
Toxicity to Reproduction	Y	Y	-	-	Y	Y	N

1. Study was conducted using the *trans* isomer of DMCD (CAS No.: 3399-22-2).
2. Endpoint was completed using 1,4-Cyclohexanedicarboxylic acid (CAS No.: 1076-97-7) as a surrogate.

JUSTIFICATION FOR USE OF DATA FROM A CHEMICAL ANALOG

As a means to reduce the number of tests that may be conducted, the EPA allows for the use of categories to group together chemicals that are structurally similar to characterize specific SIDS endpoints (USEPA 1999). Accordingly, the SIDS endpoints evaluating the potential for DMCD to induce genotoxicity (mutations and aberrations) and systemic toxicity followed repeated exposure was completed through the use of a structurally similar chemical that is believed to be a metabolite of DMCD. The analog chemical used for some endpoints was 1,4-cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7). It is fully anticipated in biological systems that of the methyl units attached to the carboxyl side chains of DMCD will undergo enzymatic cleavage to yield CHDA. While there are no data definitively demonstrating this cleavage for this particular compound, there are data that demonstrate the body's ability to cleave short to medium length alkyl chain esters located in the one and four positions on similar compounds. Specifically, the methyl units of 1,4-benzenedicarboxylic acid, dimethyl ester (dimethylterephthalate; DMT) and the ethylhexyl moieties of 1,4-benzenedicarboxylic acid, bis(2-ethylhexyl) ester are readily removed to form 1,4-benzenedicarboxylic acid (terephthalic acid; TPA). In addition, data exist on the cleavage of ester bonds with numerous other ester compounds synthesized by joining short chain alcohols and acids (eg. methyl-, ethyl-, and butyl-acetate) and various glycol ethers that have been acetylated.

From a toxicological perspective neither DMCD nor its analog acid exhibited any toxicity following repeated dietary exposures at a level of 1%. The duration of exposure was only 12 days for DMCD while it was 28 days for CHDA. Both compounds do not appear to be acutely toxic, although the methyl ester compound appears to be less toxic to males.

		
Chemical	1,4-Cyclohexanedicarboxylic acid, dimethyl ester	1,4-Cyclohexanedicarboxylic acid
CAS No.	94-60-0	1076-97-7
Acute Toxicity (LD_{50})	>5,000 mg/kg (males) Approx. 2812 mg/kg (females)	1,903 mg/kg (males) 2,263 mg/kg (females)
Repeat Dose Toxicity	No effects were noted following a 12-day dietary exposure at a level of 1%.	No effects were noted following a 28-day dietary exposure at a level of 1%.

TEST PLAN DESCRIPTION FOR EACH SIDS ENDPOINT

A. Physicochemical

Melting point - A value for this endpoint was obtained using MPBPWIN v1.40, a computer estimation model in EPIWIN (1).

Boiling Point - A value for this endpoint was obtained from a reputable textbook referenced in HSDB.

Vapor Pressure - A value for this endpoint was obtained using MPBPWIN v1.40, a computer estimation model in EPIWIN.

Partition Coefficient - A value for this endpoint was obtained using KOWIN v1.66, a computer estimation model in EPIWIN.

Water Solubility - A value for this endpoint was obtained using WSKOWIN v1.40, a computer estimation model in EPIWIN.

Conclusion: All end points haven been satisfied by the utilization of data obtained from the various physical chemical data modeling programs within the EPIWIN suite or have been satisfied by the utilization of data obtained from various textbooks referenced within the HSDB (1). The results from the utilization of the models within EPIWIN have been noted by the Agency as acceptable in lieu of actual data or values identified from textbooks (2). No new testing is required.

B. Environmental Fate

Photodegradation - A value for this endpoint was obtained using AOP v1.90, a computer estimation model in EPIWIN.

Stability in Water - A value for this endpoint was obtained using HYDROWIN v1.67, a computer estimation model in EPIWIN.

Biodegradation - This endpoint was satisfied through data derived from a study on the *trans*- isomer of DMCD (CAS No.: 3399-22-2). The study followed OECD test guideline 301-B and was conducted under GLP assurances. However, the chemical assessed was

Fugacity - A value for this endpoint was obtained using the EQC Level III partitioning computer estimation model found within EPIWIN.

Conclusion: All endpoints have been satisfied using actual data or through the utilization of Agency-acceptable estimation models. In total they are of sufficient quality to conclude that no additional testing is needed.

C. Ecotoxicity Data

Acute Toxicity to Fish - This endpoint was satisfied through data derived from a study on the *trans*- isomer of DMCD (CAS No.: 3399-22-2). The study followed established EPA guidelines (600/3-75-009 and 600/4-85/013, 3rd Ed.) but was not conducted under GLP assurances. The study quality was deemed to be "reliable with restrictions".

Acute Toxicity to Aquatic Invertebrates - This endpoint was satisfied through data derived from a study on the *trans*- isomer of DMCD (CAS No.: 3399-22-2). The study followed established EPA guidelines (600/3-75-009 and 600/4-85/013, 3rd Ed.) but was not conducted under GLP assurances. The study quality was deemed to be "reliable with restrictions".

Toxicity to Aquatic Plants - This endpoint is filled by data from an OECD TG-201 study conducted under GLP assurances. The quality of this study was deemed "reliable without restrictions".

Conclusion: All endpoints have been satisfied with data from well-conducted studies following established guidelines. The data from the fish and Daphnia studies were conducted on the pure *trans* isomer while the algae were exposed to both isomers. In total they are of sufficient quality to conclude that no additional testing is needed.

D. Toxicological Data

Acute Toxicity - This endpoint is filled by data from a study that followed OECD test guideline 401 and was conducted under GLP assurances. The quality of this study was deemed "reliable without restrictions".

Repeat Dose Toxicity - This endpoint is filled by data from 28-day dietary intake study that followed OECD guideline 407 and was conducted under GLP assurances. The chemical evaluated in this study was the structural surrogate 1,4-cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7). The quality of this study was deemed "reliable without restrictions". Data on DMCD are also presented but the study was only 2 weeks in duration.

Genetic Toxicity

Mutation - This endpoint is filled with a single study in *Salmonella typhimurium* (strains TA 98, 100, 1535, and 1537) and *Escherichia coli* (strain WP2*uvr*A). This study followed methods similar to OECD guideline 471 and was conducted under GLP assurances. The chemical evaluated in this study was the structural surrogate 1,4-cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7). The quality of this study was deemed "reliable without restrictions".

Aberration - This endpoint is filled with data from an *in vitro* study using Chinese hamster ovary (CHO) cells that followed methods similar to OECD guideline 473 and was conducted under GLP assurances. The chemical evaluated in this study was the structural surrogate 1,4-cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7). The quality of this study was deemed "reliable without restrictions".

Developmental Toxicity -	This endpoint is filled by data from a dietary exposure study in rats that followed OECD test guideline 421, and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential. The quality of this study was deemed "reliable without restrictions".
Reproductive Toxicity -	This endpoint is filled by data from a dietary exposure study in rats that followed OECD test guideline 421, and was conducted under GLP assurances. This protocol evaluates both developmental and reproductive toxicity potential. The quality of this study was deemed "reliable without restrictions".
Conclusion:	All endpoints have been satisfied with data from studies whose methods followed established guidelines, or utilized methods that were very similar and or scientifically appropriate. All studies were conducted under GLP assurances. In total, they are of sufficient quality to conclude that no additional testing is needed.

SIDS DATA SUMMARY

Data assessing the various physicochemical properties (melting point, boiling point, vapor pressure, partition coefficient, and water solubility) for DMCD were either obtained from reputable text references found in the HSDB or were estimated using the models within EPIWIN. These data indicate that DMCD is a liquid at room temperature (MP = -46.41 ^{o}C) with a very low vapor pressure (0.0822 mmHg). It has a relatively low estimated octanol to water partition coefficient (K_{ow} = 2.11) and accordingly is estimated to be only fairly soluble in water (688.7 ppm).

The assessment of the environmental fate endpoints (photodegradation, biodegradation, stability in water, and fugacity) was completed through the use of available data and estimation modeling programs within EPIWIN. As a result of its estimated K_{ow}, solubility in water, and relatively low volatility, fugacity estimations predict that DMCD will distribute primarily to soil and water. As DMCD is an ester its stability in water was assessed using the computer estimation program in EPIWIN. Results of that program predict it to have a half-life of greater than one year. Thus, it should be considered hydrolytically stable and further testing is not required. The biodegradability of DMCD (*trans* isomer; CAS No.: 3399-22-2) was determined by following OECD test guideline 301B. Results of this study demonstrated DMCD would not be readily degraded by wastewater organisms as defined by the time frames specified in the test. However, it was very close and its overall degradation at study termination was such that it would not be predicted to persist in the environment. Computer estimation models also indicate DMCD would be quite susceptible to attack by atmospheric hydroxyl radicals and would be expected to degrade in the atmosphere at a relatively fast rate with an estimated half-life of about 1.35 days. Its primary use as an industrial intermediate in the production of polymers and resins will result in minimal environmental releases.

The potential toxicity of DMCD to fish, Daphnia, and algae were determined through either well-conducted OECD or EPA guideline studies. The results of these studies indicate that fish may be sensitive to DMCD as its LC_{50} was 23 mg/L. DMCD did not appear to be toxic to the other organisms as no effects were noted at the highest concentrations tested (100 and 125 mg/L). Due to its use as an industrial intermediate, the potential for significant exposures to aqueous environments is unlikely accept under accidental conditions.

The potential to induce toxicity in mammalian species is very low. DMCD exhibited an LD_{50} value in rats of greater than 5,000 mg/kg in males and about 2,812 mg/kg in females. Results of an acute toxicity test on a pure *trans*-isomer (CAS No. 3399-22-2) was >3,200 mg/kg for both sexes. Data from a repeat exposure study in rats following OECD guidelines (TG-407) assed the toxicity of CHDA, a structural surrogate, over a 4-week period. In this study, CHDA (CAS No.: 1076-97-7) absolutely no evidence of toxicity was manifested at dietary levels up to 1.0% that resulted in doses of 871 mg/kg (males) and 894 mg/kg (females). Results of this study are identical with a shorter-term repeat dose study conducted on DMCD. In that study, male rats were exposed for 12 days at a maximum level of 1% (1,000 mg/kg) with no evidence of toxicity. The ability of DMCD to induce chromosomal damage was assessed using the structural surrogate CHDA (CAS No.: 1076-97-7). Results from mutagenicity and chromosomal

aberration studies on CHDA (CAS No.: 1076-97-7) indicate this material is not genotoxic. Developmental and reproductive toxicity endpoints were assessed simultaneously through the conduct of a developmental/reproductive toxicity study in rats that followed OECD test guidelines (TG-421). Based on the results of this study, it was concluded that DMCD was not teratogenic and did not show evidence of reproductive toxicity at the highest concentration tested in the diet (1.5%). This dietary level translates to a NOAEL of 888 mg/kg for males and 1,124 mg/kg for females.

In conclusion, the summarized hazard data indicate that this chemical should constitute a low risk to workers and the environment (if accidentally spilled). All endpoints have been completed with data of suitable quality and no new tests are being recommended. Due to its only current known use as an industrial intermediate in the formation of polymers and no known direct applications in consumer products, exposure to the general public is greatly minimized.

EVALUATION OF DATA FOR QUALITY AND ACCEPTABILITY

The collected data were reviewed for quality and acceptability following the general US EPA guidance (3) and the systematic approach described by Klimisch *et al.* (4). These methods include consideration of the reliability, relevance and adequacy of the data in evaluating their usefulness for hazard assessment purposes. This scoring system was only applied to ecotoxicology and human health endpoint studies per EPA recommendation (5). The codification described by Klimisch specifies four categories of reliability for describing data adequacy. These are:

1. Reliable without Restriction: Includes studies or data complying with Good Laboratory Practice (GLP) procedures, or with valid and/or internationally accepted testing guidelines, or in which the test parameters are documented and comparable to these guidelines.

2. Reliable with Restrictions: Includes studies or data in which test parameters are documented but vary slightly from testing guidelines.

3. Not Reliable: Includes studies or data in which there are interferences, or that use non-relevant organisms or exposure routes, or which were carried out using unacceptable methods, or where documentation is insufficient.

4. Not Assignable: Includes studies or data in which insufficient detail is reported to assign a rating, e.g., listed in abstracts or secondary literature.

REFERENCES

1. EPIWIN, Version 3.10, Syracuse Research Corporation, Syracuse, New York.

2. US EPA. (1999). The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program. OPPT, EPA.

3. USEPA (1998). 3.4 Guidance for Meeting the SIDS Requirements (The SIDS Guide). Guidance for the HPV Challenge Program. Dated 11/2/98.

4. Klimisch, H.-J., Andreae, M., and Tillmann, U. (1997). A Systematic Approach for Evaluating the Quality of Experimental Toxicological and Ecotoxicological Data. *Regul. Toxicol. Pharmacol.* 25:1-5.

5. USEPA. 1999. Determining the Adequacy of Existing Data. Guidance for the HPV Challenge Program. Draft dated 2/10/99.

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I. General Information

CAS Number: 94-60-0*
Name: 1,4-Cyclohexanedicarboxylic acid, dimethyl ester
Dimethyl cyclohexane-1,4-dicarboxylate
Dimethyl-1,4-cyclohexanedicarboxylate
Dimethyl hexahydroterephthalate
DMCD (mixed isomers)

* This CAS No. is a mixture of both *cis*- and *trans*- isomers. The chemical CAS number used for some tests was 3399-22-2, which corresponds to a pure *trans*- isomer of DMCD.

II. Physical-Chemical Data

A. Melting Point

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	
Method	
Method:	Estimation
Remarks:	
Results	
Melting point value:	-46.41 °C
Remarks:	Data is a mean of both estimation methods
References	MPBPWIN v1.40; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

B. Boiling Point

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	Purity unknown
Method	
Method:	Not Specified
GLP:	Unknown
Year:	Unknown
Results	
Boiling point value:	265 °C (mixed isomer)
Pressure:	Not stated
Remarks:	Primary reference was not obtained.
References	Lewis, R.J., Sr (Ed.). Hawley's Condensed Chemical Dictionary. 12th ed. New York, NY: Van Nostrand Rheinhold Co., 1993, 415.
Other	Data obtained from Hazardous Substances Data Bank Number: 5284. Last revision date: 20010809.

C. Vapor Pressure

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	
Method	
Method:	Estimation
Remarks:	Modified Grain method and Antoine method. Results are a mean of both methods.
Results	
Vapor pressure value:	0.0822 mmHg
Temperature:	25 ^{o}C
Remarks:	
References	MPBPWIN v1.40; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

D. Partition Coefficient

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	
Method	
Method:	Estimation
Remarks:	
Results	
Log K_{OW}:	2.11
Remarks:	
References	KOWIN v1.66; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

E. Water Solubility

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	
Method	
Method:	Estimation
Remarks:	
Results	
Value:	688.7 mg/L
Temperature:	25 ^{o}C
Description:	Slight
Remarks:	A K_{ow} of 2.11 was used in the estimation
References	WSKOW v1.40; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

III. Environmental Fate Endpoints

A. Photodegradation

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	
Method	
Method:	Estimation
Test type:	Atmospheric oxidation
Remarks:	
Results	
Temperature:	25 ^{o}C
Hydroxyl radicals reaction	
OH Rate constant:	7.9071 x 10^{-12} cm^3/molecule-sec
Half-life	1.35 Days (12-hr day; 1.5x10^6 OH/cm^3)
Ozone reaction:	No ozone reaction estimation
Remarks:	
Conclusions	Material is oxidized at a moderate rate by hydroxyl radicals in the atmosphere.
Data Quality	
Remarks:	
References	AopWin v1.90; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

B. Stability in Water

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	Test material is an ester compound
Method	
Method:	Estimation
Test type:	Aqueous base/acid-catalyzed hydrolysis
Temperature:	25 ^{o}C
Remarks:	
Results	
Total K_b for pH >8:	2.423 x 10^{-2} L/mol-sec
Half-life (pH 8):	331.018 days
Half-life (pH 7):	9.063 years
Remarks:	Material is not likely to be hydrolyzed by surface water.
References	HYDROWIN v1.67; Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210.
Other	

C. Biodegradation

Test Substance	
Test substance:	DMCD (*trans* isomer); CAS No.: 3399-22-2
Remarks:	Purity was 99.9%
Method	
Method:	OECD:TG-301B and Annex V C.5
Test type:	Ready biodegradation using the CO_2 evolution test (Modified Sturm)
GLP:	Yes
Year:	1991
Contact time:	35-days
Inoculum:	Activated sludge microorganisms (unacclimated)
Remarks:	Activated sludge was obtained from Van Lare Treatment plant in Rochester NY. Four inoculated carboys were used: one for the inoculum blank, one for a positive control (sodium benzoate), and two containing test article (tested at 10 and 20 mg/L). Microbe count of supernatant was 10^7 organisms/ml.
Results	
Total degradation at test end (Day 35):	81% (10 mg/L) and 79% (20 mg/L)
Time for 10% degrad.:	11 days
Does study meet 10-day window criteria:	No
Classification:	Results indicate material was not readily degraded (>60%) within the 10-day time frame
Breakdown products:	Not determined
Remarks:	No significant amount of CO_2 was evolved from inoculum blank. The positive control reached 60% degradation by Day 8 and 79% by test end (DOC loss was therefore 98%). DMCD was not readily biodegradable according to the definitions of this test which requires >60% degradation within the time window of 10 days, counting from the day that the observed level of biodegradation first exceeds 10%. Instead, DMCD was only degraded 54% (10 mg/L) and 48% (20 mg/L) in this time frame but considerable biodegradation did occur, however, based on 60% degradation within a 12-day time window. The end of the test on Day 35 observed 81% biodegradation of DMCD at 10 mg/L and 79% at 20 mg/L.
Conclusions	These data indicate DMCD is unlikely to persist in the environment but it may not be fully removed during wastewater treatment.
Data Quality	
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Ready Biodegradability (Modified Sturm); Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-105-043461-1, November 14, 1991.
Other	An activated sludge respiration inhibition test was conducted on *trans*-DMCD following OECD guidelines 209/1988 Annex V supplement and GLP assurances. Results determined the NOEC to be 1000 mg/L (highest dose tested). [Environmental Sciences Section, Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-620-043461-1, August 1991.

D. Transport between Environmental Compartments (Fugacity)

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	
Method	
Test type:	Estimation
Model used:	Level III Fugacity Model; EPIWIN:EQC from Syracuse Research Corporation
Remarks:	
Results	
Model data and results:	Distribution (%)
Estimated distribution and media concentration (levels II/III):	Air 1.32 Water 35.6 Soil 63.0 Sediment 0.119
Remarks:	Physical chemical values utilized in this model were default values obtained from the EPIWIN program.
Conclusions	
Data Quality	
Remarks:	
References	Meylan, W. (1993). User's Guide for the Estimation Programs Interface (EPI), Version 3.10, Syracuse Research Corporation, Syracuse, New York 13210. The Level III model incorporated into EPIWIN is a Syracuse Research Corporation adaptation of the methodology described by Mackay *et al.* 1996; *Environ. Toxicol. Chem.* **15(9)**, 1618-1626 and 1627-1637.
Other	

IV. Ecotoxicity

A. Acute Toxicity to Fish

Test Substance	
Test substance:	DMCD (*trans* isomer); CAS No.: 3399-22-2
Remarks:	Purity was 99.9%
Method	
Method:	EPA 600/3-75-009 and 600/4-85/013, 3rd Ed.
Test type:	Acute: Static w/ renewal at 48 hours
GLP:	No
Year:	1991
Species/strain:	Fathead minnow (*Pimephales promelas*)
Analytical monitoring:	Yes; temperature, pH, dissolved oxygen, alkalinity, hardness, conductivity
Exposure period:	96-Hours
Remarks:	Moderately hard reconstituted water used as control and dilution water. Two replicates of 500 mL solution in 1000 mL glass beakers containing 10, 48-day old fish used per treatment level. Test conducted at 24 ± 1 ^{o}C.
Results	
Nominal concentration:	10, 18, 32, 56, 100 mg/L
Measured concentration:	Not measured
Endpoint value:	96-hour LC_{50} = 23 mg/L
Biological observations:	No mortality was observed throughout the 96-hour exposure in the control. Several fish at the 18 & 32 mg/L treatment level exhibited loss of equilibrium
Statistical methods:	Trimmed Spearman-Karber Method
Remark:	Although concentrations were not measured, data from the algae study suggest the material remains in the test solution and does not volatilize or degrade.
Conclusions	The 96-hour LC_{50} value indicates that the test substance would be classified as "harmful to aquatic organisms" according to the European Union's labeling directive and would correspond to a "moderate concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	This was a well-documented study conducted using USEPA methodology but without concentration verification of test material.
References	Aquatic Toxicity of Trans-DMCD to *Pimephales promelas, Daphnia magna*, and *Ceriodaphnia dubia*; Young-Morgan & Associates, Franklin, Tennessee; August 1991.
Other	

B. Acute Toxicity to Aquatic Invertebrates

Test Substance	
Test substance:	DMCD (*trans* isomer); CAS No.: 3399-22-2
Remarks:	Purity was 99.9%
Method	
Method:	EPA 600/3-75-009 and 600/4-85/013, 3rd Ed.
Test type:	Acute
GLP:	No
Year:	1991
Species/strain:	Daphnia magna
Analytical monitoring:	Yes; temperature, pH, dissolved oxygen, alkalinity, hardness, conductivity
Exposure period:	48-Hours
Test details:	Moderately hard reconstituted water used as control and dilution water. Two replicates of 50 mL solution in 100 mL glass beakers containing 10 neonates were used per treatment level. Test was conducted at 24 ± 1 ^{o}C.
Remarks:	
Results	
Nominal concentration:	10, 18, 32, 56, & 100 mg/L
Measured concentration:	Not measured
Endpoint value:	48-hour LC_{50} > 100 mg/L
Biological observations:	Only one mortality in the 100 mg/L treatment was observed in the test. No mortality was observed in the control or other treatment levels
Statistical methods:	NA
Remarks:	Although concentrations were not measured, data from the algae study suggest the material remains in the test solution and does not volatilize or degrade.
Conclusions	The 48-hour LC_{50} value indicates that the test substance would not be classified according to the European Union's labeling directive and would correspond to a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	This was a well-documented study conducted using USEPA methodology but without concentration verification of test material.
References	Aquatic Toxicity of Trans-DMCD to *Pimephales promelas, Daphnia magna*, and *Ceriodaphnia dubia*; Young-Morgan & Associates, Franklin, Tennessee; August 1991.
Other	

C. Toxicity to Aquatic Plants

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	Purity was 92.9% by weight determined by GC/FID. Structure confirmed by mass spectrometric detection
Method	
Method:	OECD: TG-201
Test type:	Growth inhibition of algae
GLP:	Yes
Year:	2003
Species/strain:	*Selenastrum capricornutum*
Endpoint basis:	Cell concentrations (biomass) and growth rate
Exposure period:	72-hours
Analytical procedures:	Temperature, light intensity, rpm, and test substance concentration were assessed at the 0, 24, 48, and 72 hours. The pH was assessed at time 0 and after 72 hours.
Remarks:	The concentration of algae at Day 0 was 10^4 cells/ml.
Results	
Nominal concentration:	125 mg/L
Measured concentration:	124.6 mg/L (geometric mean)
Endpoint value:	E_bC_{50} and E_rC_{50} (0-72 hr) > 124.6 mg/L
NOEC or LOEC:	72-hour NOEC = 124.6 mg/L
Was control response satisfactory:	Yes (a 129.9 fold increase in cell number was observed within 3 days)
Statistical Methods:	NA, The statistical analysis of the data was not necessary as inhibition in biomass or growth rate was not observed.
Remarks:	A mean illumination of 741 foot-candles was maintained. The mean temperature was 24°C and pH ranged from 7.56 to 7.88. Cultures were oscillated at 100 rpm. Test substance and cell concentrations were determined at test initiation and at 24-hour intervals during the test. The exposure concentration was calculated as the geometric mean of the test substance solutions analyzed at test start and at 24-hour intervals. The test substance was stable under the conditions of the test as 2.98% loss was observed over 72 hours. No protocol deviations were noted.
Conclusions	The 72-hour E_bC_{50} and NOEC values indicate that, based on this study, the test substance would not be classified according to the European Union's labeling directive and would be classified as a "low concern level" according to the U.S. EPA's assessment criteria.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was a well-documented OECD-study conducted under GLP assurances
References	A Growth Inhibition Test with the Alga, *Selenastrum capricornutum*; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; Study No. EN-512-907570-A; February 26, 2003.
Other	

V. Toxicological Data

A. Acute Toxicity

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	Purity was not noted in report
Method	
Method:	OECD TG-401 (Annex V, test B.1)
Test type:	Acute lethality; LD_{50} estimate
GLP:	Yes
Year:	1996
Species/strain:	Rat/CD(SD)BR VAF/Plus
Route of exposure:	Oral gavage
Dose levels:	2,500, 4,000, and 5,000 mg/kg
Remarks:	There were five/sex at 5,000 mg/kg and 5 females for 2,500, 4,000 mg/kg. Animals were 7-8 weeks in age and weighed between 200-214 (males) and 155-184 (females) grams.
Results	
Value:	LD_{50} was >5,000 mg/kg (males) and approx. 2812 mg/kg for females
Deaths at each dose:	5,000 mg/kg: 2 males (Day 1) and 5 females (4 on Day 1 and 1 on Day 2).
Remarks:	Animals showed slight to severe weakness with prostration and diarrhea on Day 0. By Day 2 all surviving males appeared clinically normal. 4,000 mg/kg: 3/5 died on Day 1 and the other 2 died on Day 2. On day 0, animals exhibited slight to moderate weakness progressing to moderate weakness with reduced feces by Day 2. 2,500 mg/kg: 1/5 died on Day 1. Day 0, one animal exhibited slight weakness while all the others were clinically normal throughout the study. A gain in weight was reported for all survivors after the 2-week study observation period was complete. The cause of death for the rats was not determined although results of the gross necropsies indicated evidence of gastric irritation.
Conclusions	Material would be considered as slightly toxic.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	The study followed established guidelines and was conducted under GLP assurances.
References	Dimethyl-1,4-cyclohexanedicarboxylate, mixed isomer acute oral toxicity in the rat. Eastman Kodak Company, Rochester, NY; HAEL No.: 95-0212; January 9, 1996.
Other	The results of an acute toxicity study conducted on the *trans* isomer of DMCD (CAS No. 3399-22-2) indicated the LD_{50} as >3,200 mg/kg for both sexes with no evidence of toxicity. [Basic toxicity of trans-Dimethyl-1,4-cyclohexanedicarboxylate; Eastman Kodak Company, Rochester, NY; HS&HFL No.: 80-0296; February 18, 1981

B. Repeated Dose Toxicity

Test Substance	
Test substance:	1,4-Cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7)
Remarks:	Purity was 99.0%
Method	
Method:	OECD: TG-407 and Annex V B.7
Test type:	Repeated oral-dose toxicity
GLP:	Yes
Year:	1988
Species/strain:	Rat/Sprague-Dawley (CD(SD)BR)
Route of exposure:	Oral
Duration of test:	4-weeks
Exposure levels:	0, 0.1, 0.3, and 1.0% in diet
Sex:	Both (5/sex)
Exposure period:	Continuous in feed for 29 days
Post-exposure observation period:	None
Remarks:	Rats, were approximately 6-7 weeks in age and weighed 177 g (males) and 143 g (females) at study initiation. Animals were weighed and had detailed clinical observations recorded on Days 0, 4, 7, 14, 18, 22, and 29. Feed intake was assessed twice/week. At termination hematology (Hb conc., Hct, RBC count and morphology, WBC count and diff., and plt. Count) and clinical chemistries (AST, ALT, SDH, ALK, Creat., BUN, and gluc.) were conducted. At termination, animals underwent a gross examination with the following organs weighed: liver, spleen, kidneys, adrenals, testes, and thymus. Organs examined by histology included: trachea, lungs, heart, esophagus, stomach, sm. & lg. intestine, pancreas, liver, salivary glands, kidney, urinary bladder, pituitary, adrenals, thyroids, parathyroids, thymus, spleen, mesenteric lymph nodes, bone marrow, brain, testes, epididymis, accessory sex organs in males, fallopian tubes, uterus, vagina and ovaries.
Results	
NOAEL (NOEL):	1.0%; [871 mg/kg (males) and 894 mg/kg (females)]
Actual doses received:	Males: 0, 81, 246, 871 mg/kg; Females: 0, 86, 259, 894 mg/kg
Toxic responses by dose:	There were no mortalities or clinical signs related to exposure. There were no differences in body weights, feed consumption, hematology, clinical chemistries, and organ weights compared to controls. There were no gross or histological changes observed.
Statistical methods:	Mean values of most data were evaluated for homogeneity by Bartlett's test and significance assessed using ANOVA and Duncan's multiple range test.
Remarks:	
Conclusions	CHDA induced essentially no toxicity following 4 weeks of exposure at a high exposure rate (1% of diet).
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This is a well-documented study that followed OECD guidelines and was conducted under GLP assurances.
References	Four-Week Oral Toxicity Study of 1,4-Cyclohexanedicarboxylic Acid in the Rat. Eastman Kodak Company, Rochester, NY; HAEL No.: 87-0082, Experiment No.: 870082F1, January 8, 1988.
Other	

Test Substance	
Test substance:	DMCD (*trans* isomer); CAS No.: 3399-22-2
Remarks:	Purity was unknown, material was stated to have 1.6% of the *cis*- isomer
Method	
Method:	Other
Test type:	Repeated oral-dose toxicity
GLP:	No
Year:	1981
Species/strain:	Rat/
Route of exposure:	Oral
Duration of test:	2-Weeks
Exposure levels:	0, 0.1 and 1.0% in diet
Sex:	Male
Exposure period:	Continuous in feed for 12 days
Post-exposure observation period:	None
Remarks:	Five rats were exposed to trans-DMCD in their diet. Observations were made of body weight, feed consumption, clinical signs, hematology (Hb conc., Hct, RBC count and morphology, WBC count and diff.) and clinical chemistries (AST, ALT, LDH, ALK, Creat., BUN, and gluc.) were conducted. At termination, animals underwent a gross examination with the liver and kidneys weighed and examined histologically.
Results	
NOAEL (NOEL):	1.0%; 1000 mg/kg
Actual doses received:	0, 97, and 1000 mg/kg
Toxic responses by dose:	There were no mortalities or clinical signs related to exposure. There were no differences in body weights, feed consumption, hematology, clinical chemistries, and organ weights compared to controls. There were no gross or histological changes observed.
Statistical methods:	Not described.
Remarks:	
Conclusions	Trans-DMCD induced essentially no toxicity following 2 weeks of exposure at a high exposure rate (1% of diet).
Data Quality	
Reliability:	Reliable with restrictions
Remarks:	Only basic data as part of a report summary were available for this study and significant methodological details were not present.
References	Basic Toxicity of *trans*-Dimethyl-1,4-cyclohexanedicarboxylate. Eastman Kodak Company, Rochester, NY; HS&HFL No.: 80-0296, February 18, 1981.
Other	

C. Genetic Toxicity - Mutation

Test Substance	
Test substance:	1,4-Cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7)
Remarks:	Purity unknown
Method	
Method:	Other; OECD: TG-471-like
Test type:	*In vitro* mutagenicity
GLP:	Yes
Year:	1994
Species/strain:	*Salmonella typhimurium* (strains: TA98, 100, 1535, and 1537) and Escherichia *coli* (strain: WP2*uvr*A(pKM101)
Metabolic activation:	Yes; Sprague-Dawley rat liver S9 induced with Aroclor 1254
Concentration tested:	100, 333, 667, 1,000, 3,330, and 5,000 ug/plate
Remarks:	Positive controls: 2-aminoanthracene, 2-nitrofluorene, sodium azide, ICR-191, 4-nitroquinoline-N-oxide. Negative control was the test vehicle dimethylsulfoxide. The study was performed in triplicate at each dose.
Results	
Result:	No positive responses were induced by CHDA in any of the tester strains
Cytotoxic concentration:	No cytotoxicity was observed
Precipitation concentration:	No precipitate was noted.
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Specific methods were not noted in the report. However, analyses were not needed due to the absence of an increase in the number of revertants colonies at any dose beyond the positive control.
Remarks:	
Conclusions	Material was not genotoxic under conditions of this assay.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was well-documented study that followed the basic principles of those outlined in OECD guideline 471 and was conducted under GLP assurances. Data were missing on sample purity.
References	Mutagenicity Test with EC 94-0212, CHDA in the Salmonella – Escherichia coli/Mammalian-Microsome Reverse Mutation Assay with a Confirmatory Assay; Hazelton Washington, Vienna, VA; HWA Study No.: 16281-0-409R; September 19, 1994.
Other	

D. Genetic Toxicity – Chromosomal Aberrations

Test Substance	
Test substance:	1,4-Cyclohexanedicarboxylic acid (CHDA; CAS No.: 1076-97-7)
Remarks:	Purity unknown
Method	
Method:	Similar to OECD: TG-473
Test type:	*In vitro* mammalian chromosomal aberrations assay
GLP:	Yes
Year:	1994
Species/strain:	Chinese hamster ovary cells (CHO)
Concentrations tested:	750, 1,000, 1,500, and 2,000 ug/ml
Metabolic Activation:	Aroclor 1254-induced SD rat liver S9
Remarks:	The positive controls consisted of mitomycin-C and cyclophosphamide. Negative control was the test vehicle dimethylsulfoxide. Assay length was 20.0 hours. Replicate cultures were used at each dose level. Mitotic index was based on metaphase analysis of 1000 cells and aberrations were based on a scoring of 100 cells from each replicate or 200 total.
Results	
Result:	No significant increase in cells with aberrations was observed (see remarks)
Cytotoxic concentration:	Evidence of cytotoxicity was seen at 2,250 ug/ml
Precipitation concentration:	A precipitate was observed at the 2,250 ug/ml concentration
Genotoxic effects	
With activation:	Negative
Without activation:	Negative
Statistical methods:	Statistical analysis employed a test for linear trends and Fisher's Exact Test to compare the percentage of cells with aberrations with an adjustment for multiple comparisons.
Remarks:	A confirmatory assay was conducted at dose levels of 500, 1,000, 1,500, 2,000, and 2,250 ug/ml with cells harvested after 20 and 44 hours. Complete toxicity was seen at 2,250 ug/ml without metabolic activation. No increases in aberrations were seen after 20 hours in the non-activation system or at 44 hours with S9 at any dose. However, an increase in aberrations was seen in one of the replicates at the 2,000 ug/ml dose (-S9) at the 44-hour time point and at the 2,250 ug/ml dose with S9 after 20 hours. A significant increase in percent polyploidy was observed at 2,250 ug/ml from the 44-hour assay with activation.
Conclusions	No dose relationship was observed in the assays where a positive response was observed. The positive response for aberrations was observed in only one of the replicate cultures while the Polyploidy response was seen in both. However, severe toxicity was seen at this concentration. Accordingly, the relevance of these effects at a toxic concentration makes its significance questionable.
Data Quality	
Reliability:	Reliable without restrictions
Remarks:	This was well-documented study that followed the basic principles of those outlined in OECD guideline 473 and was conducted under GLP assurances. Data were missing on sample purity.
References	Measuring Chromosomal Aberrations in Chinese Hamster Ovary Cells; Hazelton Washington, Vienna, VA; HWA Study No.: 16281-0-437CO; November 1, 1994
Other	

E. Developmental Toxicity

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	Purity was 93.2%
Method	
Method:	OECD:TG-421; USEPA: OPPTS 870.3550
GLP:	Yes
Year:	2003
Species/strain:	Rats/Sprague-Dawley CRL:CD®(SD)IGS BR
Sex:	Male and Female (12/sex/exposure level)
Route of exposure:	Oral, dietary
Exposure levels:	0, 1.5, 4.5, and 15.0 mg/g of feed (0.15, 0.45, and 1.5%)
Actual dose levels:	Approx. 92, 276, and 888 mg/kg (male), and 111, 351, and 1124 mg/kg (female)
Exposure period:	24 hrs/day; Test material in diet was fed *ad libitum*
Frequency of treatment:	7 days/week
Control group and treatment:	Controls were exposed to basal diet
Duration of test:	The study consisted of four phases: pre-mating (14 days); mating (1 to 14 days); pregnancy (21 to 23 days); and early lactation (4 to 6 days). The male rats were treated throughout the study, a period of 50 days. The female rats were treated throughout the study until they were euthanized, a period of approximately 38-57 days. The male rats were euthanized on Day 51. The female rats that delivered a litter, and their offspring, were euthanized on Days 4, 5, or 6 postpartum. Female rats that showed evidence of mating but did not deliver were euthanized on Day 23 of gestation.
Remarks:	The study design included the additional endpoints of epididymal spermatozoan numbers and motility, and testicular spermatid head counts.
Results	
Maternal/Paternal toxicity	
NOAEL:	1.5%; or 888 mg/kg for males and 1124 mg/kg for females
Repro./Develop. toxicity	
NOAEL:	1.5%; or 888 mg/kg for males and 1124 mg/kg for females
Parental toxic responses:	Male rats that consumed diets containing 15.0 mg/g (1.50%) of the test substance exhibited reduced mean body weights and/or feed consumption values for the duration of the study. However, there were no adverse effects on fertility, histology of the testes and epididymis, or testicular and epididymal sperm counts. No treatment-related effects were seen in male rats from the lower dose groups. There were no treatment-related effects or histopathological alterations seen in female rats from any dose group and there were no biologically significant changes in their offspring.
Postnatal toxic responses:	There were no toxicologically significant differences in the reproductive parameters evaluated including reproductive performance, fertility index, fecundity index, precoital interval, gestation duration, numbers of implants, number of corpora lutea, pre- and post-implantation loss, pup survival, live and dead pups, male and female pups, pup body weight and body weight changes. Although the duration of the gestation phase was shorter ($p \leq 0.05$) for female rats from the mid-dose group, there was no apparent effect on pup viability. Mean pup weight change and percent pup weight change from Days 0 to 4 were also significantly ($p \leq 0.05$) higher for pups from the low-dose group when compared with the control group, but these changes were not considered biologically significant.

Statistical Methods:	Homogeneity of data was evaluated using Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Dunnett's t-test ($p \leq 0.05$) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test ($p \leq 0.01$), the data were evaluated using a Kruskal-Wallis H-test ($p < 0.05$) followed by Mann-Whitney U-test ($p < 0.05$).
Remarks:	The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test ($p < 0.05$).
Conclusions	DMCD did not affect the reproductive capacity of the adult animals in this study.
Data Quality	
Reliability:	Reliable without restriction
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; July 2003.
Other	

F. Reproductive Toxicity

Test Substance	
Test substance:	DMCD (mixed isomers); CAS No.: 94-60-0
Remarks:	Purity was 93.2%
Method	
Method:	OECD:TG-421; USEPA: OPPTS 870.3550
GLP:	Yes
Year:	2003
Species/strain:	Rats/Sprague-Dawley CRL:CD®(SD)IGS BR
Sex:	Male and Female (12/sex/exposure level)
Route of exposure:	Oral, dietary
Exposure levels:	0, 1.5, 4.5, and 15.0 mg/g of feed (0.15, 0.45, and 1.5%)
Actual dose levels:	Approx. 92, 276, and 888 mg/kg (male), and 111, 351, and 1124 mg/kg (female)
Exposure period:	24 hrs/day; Test material in diet was fed *ad libitum*
Frequency of treatment:	7 days/week
Control group and treatment:	Controls were exposed to basal diet
Duration of test:	The study consisted of four phases: pre-mating (14 days); mating (1 to 14 days); pregnancy (21 to 23 days); and early lactation (4 to 6 days). The male rats were treated throughout the study, a period of 50 days. The female rats were treated throughout the study until they were euthanized, a period of approximately 38-57 days. The male rats were euthanized on Day 51. The female rats that delivered a litter, and their offspring, were euthanized on Days 4, 5, or 6 postpartum. Female rats that showed evidence of mating but did not deliver were euthanized on Day 23 of gestation.
Remarks:	The study design included the additional endpoints of epididymal spermatozoan numbers and motility, and testicular spermatid head counts.
Results	
Maternal/Paternal toxicity	
NOAEL:	1.5%; or 888 mg/kg for males and 1124 mg/kg for females
Repro./Develop. toxicity	
NOAEL:	1.5%; or 888 mg/kg for males and 1124 mg/kg for females
Parental toxic responses:	Male rats that consumed diets containing 15.0 mg/g (1.50%) of the test substance exhibited reduced mean body weights and/or feed consumption values for the duration of the study. However, there were no adverse effects on fertility, histology of the testes and epididymis, or testicular and epididymal sperm counts. No treatment-related effects were seen in male rats from the lower dose groups. There were no treatment-related effects or histopathological alterations seen in female rats from any dose group and there were no biologically significant changes in their offspring.
Postnatal toxic responses:	There were no toxicologically significant differences in the reproductive parameters evaluated including reproductive performance, fertility index, fecundity index, precoital interval, gestation duration, numbers of implants, number of corpora lutea, pre- and post-implantation loss, pup survival, live and dead pups, male and female pups, pup body weight and body weight changes. Although the duration of the gestation phase was shorter ($p \leq 0.05$) for female rats from the mid-dose group, there was no apparent effect on pup viability. Mean pup weight change and percent pup weight change from Days 0 to 4 were also significantly ($p \leq 0.05$) higher for pups from the low-dose group when compared with the control group, but these changes were not considered biologically significant.

Statistical Methods:	Homogeneity of data was evaluated using Bartlett's test ($p \leq 0.01$), one-way analysis of variance (ANOVA) ($p \leq 0.05$), and Dunnett's t-test ($p \leq 0.05$) to indicate statistical significance. When the variances of the means were not considered equal by the Bartlett's test ($p \leq 0.01$), the data were evaluated using a Kruskal-Wallis H-test ($p < 0.05$) followed by Mann-Whitney U-test ($p < 0.05$).
Remarks:	The reproductive performance of the dams and the fertility and fecundity indices were evaluated in contingency tables, using a Chi-square test ($p < 0.05$).
Conclusions	DMCD did not affect the reproductive capacity of the adult animals in this study.
Data Quality	
Reliability:	Reliable without restriction
Remarks:	This was a well-documented OECD guideline study conducted under GLP assurances.
References	Reproduction/Developmental Toxicity Screening Test in the Rat. Toxicological Sciences Laboratory; Health and Environment Laboratories, Eastman Kodak Company, Rochester, NY; July 2003.
Other	